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REMARKS

Claims 1-42 were pending in the application. Claims 2, 4, and 14-39 are canceled herein as being directed to non-elected inventions. Claims 1 and 3 have been amended. Support for the amendments to the claims can be found, for example, in claims 4 and 5 as filed. No new matter has been added.

Rejection of Claims 1, 3, 5-13 and 40-42 Under 35 USC 112, First Paragraph

The Examiner has rejected claims 1, 3, 5-13, and 40-42 because, "while being enabling for an antibody generated against [a] peptide of at least 6 amino acids" the Examiner believes that the specification "does not reasonably provide enablement for [an] antibody generated against a peptide of 3 amino acids." Applicants respectfully traverse this rejection.

Applicants have elected antibodies that recognize a peptide comprising 1st to 3rd amino acid residues of SEQ ID NO:4. Applicants believe that these antibody are fully enabled by the specification as filed. The Examiner argues that antibodies will not recognize peptides of only three amino acid residues, but that at least six amino acid residues are necessary.

The pending claims are directed to antibodies that recognize polypeptides that comprise the 1st to 3rd amino acid residues of SEQ ID NO:4. Cleary these claims encompass peptides that comprise these specific residues but are longer than three amino acid residues. The fact that some of the species in this genus of peptides are not recognized by the antibodies does not mean that the claims are not enabled by the specification. Specifically, the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled. The standard is whether a skilled person could

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determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Atlas Powder Co. v. E.I. duPont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

In the instant case, the inoperative embodiments could easily be determined using a simple assay.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the foregoing enablement rejection.

Application No. 10/557,351
Amendment dated July 2, 2009
Reply to Office Action of April 2, 2009

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Docket No.: 64476(46342)

Rejection of Claims 8-13 Under 35 USC 112, First Paragraph

The Examiner has rejected claims 8-13 under 35 USC 112, first paragraph as not being described in such a way as to enable one skilled in the art to make and/or sue the invention. The Examiner states that a deposit of the cell AhW23N2G6D1 and AhW23N3H3E4 is required to enable the invention of claim 8 and 11, and that if a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or the like should be required. Applicants respectfully traverse this rejection.

Applicants respectfully submit International Forms ("Receipts") and translations thereof for FERM BP-8363 and for FERM BP-8364. As shown in the specification and in the Receipts, both deposits were made with the International Patent Organisms Depository, National Institute of Advanced Industrial Science and Technology (formerly, National Institute of Bioscience and Human-Technology (NIBH)), located at 1-1 Higashi 1-chome, Tsukuba-shi, Ibaraki-ken (postal code: 305-8566), Japan, and receipt was acknowledged on April 23, 2003, which is before the effective filing date of the application for a patent in the United States. The microorganisms and cell lines described in the above application, to which reference is made in the claims, have the following accession numbers and dates of deposit, as shown on the attached Receipts in Case of an Original Deposit (with translations):

<u>Microorganism/Cell Line</u>	<u>FRI</u>
AhW23N2G6D1	FERM BP-8363
AhW23N3H3E4	FERM BP-8364

Pursuant to 37 C.F.R. §1.808, Applicants have confirmed that (1) access to the deposit will be available during pendency of the patent application making reference to the deposit to one determined by the Director to be entitled thereto; and (2) subject to paragraph (b) of 37 C.F.R. §1.808, all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the patent. Applicants note that the FRI is currently the National Institute of

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Advanced Industrial Science and Technology (formerly, National Institute of Bioscience and Human-Technology (NIBH)), which is an International Depositary Authority recognized by the Budapest Treaty as specified under 37 C.F.R. §1.803. During the pendency of this application, access to the invention will be afforded to the Commissioner upon request. Applicants submit that all restrictions on the availability to the public of the culture deposited will be irrevocably removed upon the granting of a patent from the above-identified application. Applicants also submit that the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the enforceable life of the patent, whichever is longer and that the deposit will be replaced if it should ever become nonviable.

Accordingly, Applicants respectfully submit that the Examiner reconsider and withdraw the foregoing rejection..

Rejection of Claims 1, 3, 5-7 and 40-42 Under 35 USC 102(b) and (e)

The Examiner has rejected claims 1, 3, 5-7 and 40-42 under 35 USC 102(b) as allegedly being anticipated by Torigoe et al. (US6,087,116). The Examiner has also rejected claims 1, 3, 5-7 and 40-42 under 35 USC 102(e) as allegedly being anticipated by Mori et al. (US 7,193,033). Applicants respectfully traverse these rejections.

Claim 1 is directed to a monoclonal antibody which specifically reacts with a partial peptide at the N-terminal region of a polypeptide or a salt thereof, wherein the polypeptide comprises the amino acid sequence represented by SEQ ID NO: 4; and does not recognize the partial peptide at the C-terminal region of a polypeptide or a salt thereof, wherein the polypeptide comprises the amino acid sequence represented by SEQ ID NO: 4; and having a neutralizing activity for a peptide comprising the amino acid sequence represented by SEQ ID NO: 4.

Torigoe et al. and Mori do not teach, or even suggest, the claimed monoclonal antibody, particularly having the technical features, i.e., capability of reacting with the partial peptide at the N-terminal region of a protein of SEQ ID NO: 4; but not recognizing the partial peptide at the C-terminal region.

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The Examiner states that the antibody inherently has the neutralizing activity since it binds the polypeptide. However, depending upon differences in recognition sites, some antibodies may have neutralizing activity against its antigen protein, and some antibodies may not have the neutralizing activity. This is common technical knowledge to a skilled person in the art in the fields of antibodies. Applicants submit herewith a copy of Regulatory Peptides 54 (1994) 439-444. This scientific paper describes that two out of four antibodies (NYP02, NYP03, NPY04 and NPY05) prepared exhibited a neutralizing activity, i.e., activity to inhibit binding of neuropeptide Y (NYP) to its receptor. As described in the abstract, NPY02 and NPY05 block the binding of NPY to its receptor as well as the NPY-induced inhibition of cAMP accumulation caused in SK-N-MC cells by forskolin, while NPY03 and NPY04 inhibit the binding of NPY only at very high concentrations and have a weak effect on cAMP response to NYP (see Abstract, lines 3-7). Based on the results described in this reference and others known to those of skill in the art, it is clear that not all antibodies have a neutralizing activity against their antigen protein.

Accordingly, the present antibody capable of recognizing the N-terminus of SEQ ID NO: 4 and not recognizing the C-terminus and having a neutralizing activity against the protein of SEQ ID NO: 4, is not anticipated by any one of the cited references which do not describe such recognition site and the neutralizing activity.

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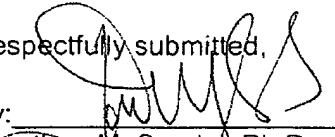
Conclusion

In view of the above amendment, applicant believes the pending application is in condition for allowance.

Dated: July 2, 2009

Respectfully submitted,

By:


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BOS2 744589.1



Interactions between NPY and its receptor: assessment using anti-NPY antibodies

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Abstract

The present data show that monoclonal antibodies (NPY02, NPY03, NPY04, NPY05) directed against 4 distinct epitopes on NPY may have different actions on NPY binding and NPY-induced cellular responses. NPY02 and NPY05 recognize the 11–24 and 32–36 amidated form of NPY, respectively. These 2 antibodies block the binding of NPY to its receptor as well as the NPY-induced inhibition of cAMP accumulation caused in SK-N-MC cells by forskolin. NPY02 and NPY05 have also an inhibitory action on NPY-induced contraction of rabbit femoral arteries. NPY03 and NPY04 are directed against the 27–34 and 1–12 part of NPY, respectively. NPY03 and NPY04 inhibit the binding of NPY only at very high concentrations and have a weak effect on cAMP response to NPY. NPY02 and NPY05 might provide useful tools to study the effect of NPY in cellular systems and organ preparations.

Keywords: Neuropeptide Y; Y1 receptor; Anti-NPY antibody

1. Introduction

Neuropeptide Y is a 36 amino-acid peptide isolated from porcine brain in 1982 [1]. This peptide acts through specific receptors belonging to the family of G protein coupled receptors [2]. NPY might be involved in the cardiovascular regulation by exerting a direct vasoconstrictor action as well as by potentiating the contractile response to norepi-

nephrine and angiotensin II [3,4]. In addition, NPY inhibits pre-synaptically the release of norepinephrine [5]. The N and C terminal residues of NPY are tyrosine and tyrosinamide, respectively. These terminal parts of the molecule are necessary for the binding to the Y1 receptor sub-type and the resulting activation of intracellular second messenger systems. On the other hand, the 13 to 36 fragment of NPY can act pre-synaptically on the Y2 receptor sub-type [5]. The human Y1 receptor has recently been cloned [6,7].

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taken out, dissected free of connective tissue and cut in 2 mm wide rings. The rings were then carefully suspended under a tension of 500 mg between 2 parallel hooks in 10 ml organ baths containing a physiological salt solution of the following composition (mM): NaCl 112.0, KCl 5.0, Na₂CO₃ 25.0, NaH₂PO₄ 1.2, CaCl₂ 2.5, glucose 11.2. The solution was maintained at 37° and gassed with 95% O₂ and 5% CO₂ to obtain a pH of 7.4. Contractile responses were measured with an isometric strain gauge (Biegestab K30, Hugo Sachs Elektronik, Freiburg, Germany) coupled to a potentiometric pen recorder (Lineacord Mark VII, WR 3101, Hugo Sachs Elektronik).

After a 60 min equilibration period (during which the tension was readjusted to 500 mg), the rings were maximally contracted with noradrenaline (NA) 10⁻⁵ M, then washed and, 30 min later, contracted with NA 10⁻⁷ M and relaxed with acetylcholine 10⁻⁷ M to control the integrity of the endothelium. Preparations were washed and left for a further 45 min equilibration. One of the 4 monoclonal antibodies (MAb) at a concentration of 10⁻⁷ M was added to the bath and after 20 min incubation, a cumulative dose-response curve with NPY (10⁻⁸ to 3 · 10⁻⁷ M) was performed.

Statistical analysis of the results was done using analysis of variance or *t*-test. The individual variations were analyzed by the Fisher's protected test. Data are shown as means ± 1 S.D.

3. Results

3.1. Radioreceptor assay of NPY

The radioreceptor assay with SK-N-MC cells provided a total binding equal to 10% of the radioactivity added to the wells and a specific binding of 82 ± 5%. Scatchard experiments showed an apparent affinity constant at about 0.6 nM with 100,000 binding sites per cell (data not shown). The binding was time dependent and reached a plateau within 1 h.

3.2. Radioreceptor assay of NPY in the presence of anti-NPY monoclonal antibodies

Preincubation of NPY with increasing amounts of the MAbs had 2 different effects on the binding of NPY to its receptor (Fig. 1).

(1) NPY03 and NPY04 affected the binding of NPY to its receptor only at the highest antibody concentration (1 µg/well)

(2) NPY02 blocked completely and NPY05 partially the binding of NPY. The Fab of NPY 05 was as active as the whole immunoglobulin (not shown).

The anti-angiotensin II antibody did not alter the NPY binding.

3.3. Determination of cAMP accumulation in SK-N-MC cells

The effect of anti-NPY MAbs on the inhibition by NPY of the forskolin-induced cAMP accumulation is shown in Fig. 2. Baseline levels of cAMP measured in the absence of NPY were 23.9 ± 1.0, 19 ± 0.1, 19.7 ± 2.6, 23.7 ± 0.9, 28.9 ± 3.0, 30.3 ±

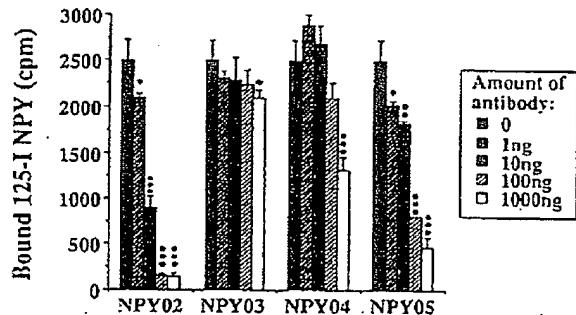


Fig. 1. Effects of 4 NPY antibodies (NPY02, NPY03, NPY04, NPY05) on the binding of ¹²⁵I-NPY to its receptor on SK-N-MC cells. Different amounts (1, 10, 100 or 1000 ng) of these monoclonal antibodies were preincubated for 4 h with ¹²⁵I-NPY prior to the receptor assay. Data is expressed as bound cpm of iodinated NPY (mean ± S.D.). Four separate experiments were performed and the measurement done in triplicate. *P<0.05; **P<0.01; ***P<0.001, versus control values.

The NPY structure is highly conserved. The sequence is identical among different species such as human, rat, dog and rabbit with the exception of the porcine NPY which has a leucine instead of a methionine in position 17 [8]. The proposed model of NPY exhibits a polyproline helix (residues 1–8) followed by a tight hairpin and an antiparallel α helix (aminoacids 13 to 32) ending in a short terminal tetrapeptide amide spatially close to the N-terminal portion [9]. In vitro analysis of structure-function relationships of NPY have shown that the 25–36 region of NPY, and particularly the amidated C-terminus, Arg³³ and Arg³⁵, as well as the Gln³⁴ and His³⁶ residues are essential for the biological activity of NPY whereas the Tyr¹ side chain seems to be of less importance [10–12].

We have isolated and characterized 4 anti-NPY monoclonal antibodies (Mabs) [13] and then identified their epitopes. The goal of the present investigation was to define the interaction between NPY and the Y1 receptor by identifying some regions of the peptide critically involved in receptor binding. For this purpose we used our 4 anti-NPY monoclonal antibodies NPY02, NPY03, NPY04 and NPY05.

2. Materials and methods

2.1. Radioreceptor assay of NPY

The radioreceptor assay of NPY was performed using SK-N-MC cells, a human neuroblastoma cell line expressing NPY Y1 receptors [14]. The cells were obtained from American Type Culture Collection (Rockville, USA).

Cells were plated in 24 well plates (Costar, ref. 3424, Cambridge, MA, USA) until they reached confluence. At that time, a non-saturating amount of ¹²⁵I-NPY (50 pM, Amersham, specific activity 2000 Ci/mmol) and various amounts of cold peptide were added. Incubation was performed for one hour at room temperature in 300 μ l of EMEM (Eagle's

minimum essential medium) supplemented with 5 mM CaCl₂, 10 mM Hepes, 0.5% bovine serum albumin and 1 mg/ml bacitracine (binding buffer). After washing twice with 500 μ l binding buffer, the cells were lysed with 500 μ l lysis solution (urea 48% (w/v), Nonidet P 40 2% (v/v), acetic acid 17.2% (v/v)). The bound radioactivity was then determined in a gamma counter. Non specific binding was estimated in the presence of 1 μ M unlabelled NPY.

2.2. Radioreceptor assay of NPY in the presence of anti-NPY monoclonal antibodies

Anti-NPY Mabs were preincubated for 4 h at room temperature with iodinated NPY in binding buffer. The mixture was then added to the cells and the binding measured as described above. The same procedure was repeated with an anti-angiotensin II Mab (F79) as a control.

2.3. Determination of cAMP accumulation in SK-N-MC cells

NPY is known to inhibit forskolin stimulated cAMP accumulation [14]. SK-N-MC cells grown in 6-well plates were incubated in the presence of different concentrations of NPY or [NPY–Mab] complexes for 1 h in 1 ml of binding buffer supplemented with 10 μ M forskolin and 10 μ M papaverin. Binding of antibodies to NPY was adjusted to about 40% as determined by radioimmunoassay. The cells were then washed with phosphate-buffered saline and lysed by 750 μ l 0.1 M HCl. Cell debris were removed by centrifugation at 1200 g for 10 min. The supernatant was lyophilised and cAMP content evaluated by a radioimmunoassay kit (Amersham single range assay system RPA 508).

2.4. In vitro studies on isolated arteries

Male Chinchilla rabbits (Dr. Thomae, Bibcrach a.d. Riss, Germany), weighing 2.5 to 3 kg, were killed by a blow to the neck. Both femoral arteries were

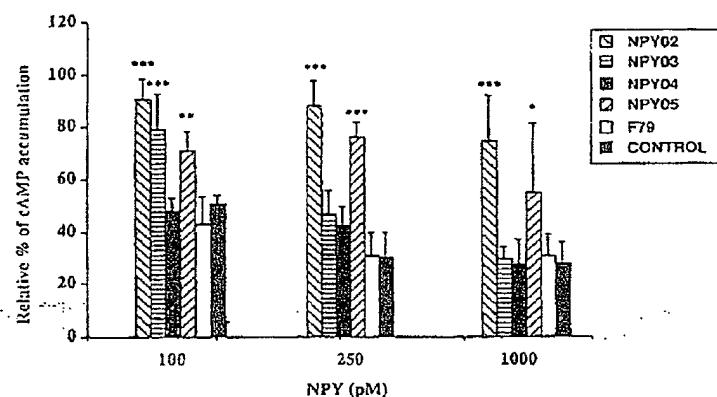


Fig. 2. Effect of anti-NPY antibodies (NPY02, NPY03, NPY04, NPY05) on the inhibition by NPY of the forskolin-induced cAMP accumulation. The anti-angiotensin II monoclonal antibody F79 was used as an irrelevant antibody and control experiments were performed in absence of MAb. Results are expressed as % of the total cAMP accumulation induced by forskolin, 10 μ M; in the absence of NPY. Three doses of NPY were tested (100, 250 or 1000 pM) and the results represent the mean \pm S.D. of 3 to 5 separate experiments. The measurements were done in triplicate. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, versus the corresponding control values.

1.5 pmol/well in the control, NPY02, NPY03, NPY04, NPY05 and anti-angiotensin II MAb experiments, respectively. No significant difference was observed between the baseline measurements obtained with the various MAbs. These levels were used as 100% values. NPY inhibited the forskolin-induced cAMP accumulation in a dose-dependent fashion. NPY02, NPY03 as well as NPY05 had an inhibitory effect of this NPY action. NPY02 was in this respect the most potent since effective blockade of the forskolin-induced cAMP accumulation was still seen with the highest doses of NPY, doses at which no inhibition was observed with NPY03 and NPY05. Regarding NPY04, like the anti-angiotensin II MAb F79, it did not affect the NPY inhibitory action.

3.4. In vitro studies on isolated arteries

In the rabbit femoral artery, NPY produced a dose-dependent increase in tension. The threshold concentration of NPY was 10^{-8} M and a maximal contraction (194 ± 20 mg) was reached at a con-

centration of $3 \cdot 10^{-7}$ M. None of the 4 MAbs had any effect by itself on the basal tension of the ring.

The MAb NPY02 (10^{-7} M) prevented the tension development induced by NPY at concentration of 10^{-8} M to 10^{-7} M. At a higher concentration of NPY ($3 \cdot 10^{-7}$ M), a contraction appeared which was of similar magnitude (172 ± 52 mg) as under control conditions. NPY05 had an effect nearly similar to NPY02. On the contrary, NPY03 and NPY04, even at concentrations of 10^{-7} M, did not significantly alter the contraction produced by NPY (Fig. 3).

4. Discussion

These studies were undertaken to assess the impact of various anti-NPY monoclonal antibodies on the binding and the cellular responses to NPY. This was done with antibodies having well defined epitopes, which should give valuable information on the regions of NPY involved in the binding and the actions of the peptide. The experiments were per-

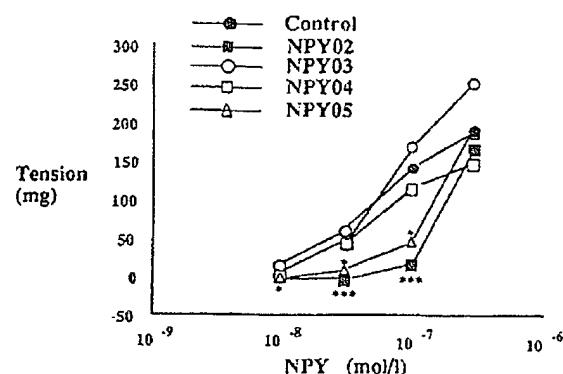


Fig. 3. In vitro effect of anti-NPY monoclonal antibodies ($0.1 \mu\text{M}$) on NPY-induced contraction of rabbit femoral arteries.
* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, versus control values. Control $n = 18$; NPY02 $n = 6$; NPY03, NPY04 and NPY05 $n = 4$.

formed in SK-N-MC cells, i.e., a human neuroblastoma cell line known to express the Y1 sub-type of NPY receptor [14]. The characteristics of our 4 monoclonal antibodies have been described elsewhere [13] and are illustrated in Fig. 4. NPY04 recognizes the 1–12 region of NPY and does not cross-react with peptide YY (PYY) or pancreatic polypeptide (PP). NPY02 antibody is directed against the hairpin 11–24 region of NPY and does not bind to PYY and PP. NPY03 and NPY05 are directed against the C terminal (27–34 and 32–36 amidated NPY, respectively) and both bind to PYY. NPY05 but not NPY03 recognizes PP. K_d for the 4 monoclonal antibodies are within the same nanomolar range (Fig. 4).

NPY02 and NPY05 caused a dose-dependent in-

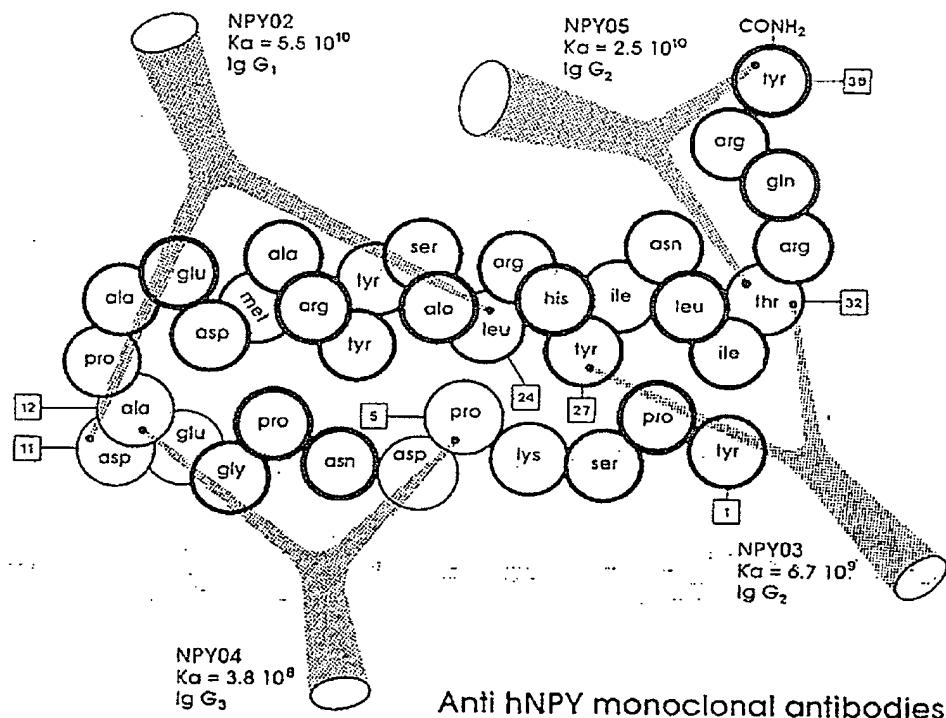


Fig. 4. Epitopes of NPY recognized by the four anti-NPY monoclonal antibodies (from Ref. [13]).

hibition of NPY binding. This effect might be due to the fact that both the hairpin loop and the C-terminal of the peptide are essential for the recognition of NPY by its receptor; however, we cannot exclude a possible steric hindrance caused by these antibodies on NPY binding. NPY02 and NPY05 both blocked the second messenger responses to NPY, as assessed by the NPY-induced inhibition of forskolin-stimulated cAMP accumulation. The two antibodies had also an inhibitory action in a vascular preparation on the contractile response to NPY. This effect was dose-dependent and more potent for NPY02 than for NPY05.

NPY03 inhibited the binding of NPY only at very high concentrations. With regard to the cAMP response, it was slightly altered by NPY03 only at the lowest test dose of NPY.

NPY04 had an inhibitory effect on NPY binding only at high concentration, but this was not associated with any effect on cellular and vasoconstrictor responses to NPY.

In conclusion, the present data show that monoclonal antibodies directed against various epitopes of NPY may have different actions on NPY binding and NPY-induced cellular responses. Some of these well-characterized antibodies provide therefore useful tools to study the effect of NPY in cellular systems and organ preparations.

5. Acknowledgements

This work was supported by grants from the Swiss National Science Foundation, Ciba-Geigy Ltd. and the Cardiovascular Research Foundation.

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BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITORY AUTHORITY
identified at the bottom of this page

To: Depositor

Name: Takeda Pharmaceutical Company Limited
Kunio Takeda
Representative

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi

1. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR: Accession number given by the INTERNATIONAL DEPOSITORY AUTHORITY

Ab#23N3H3E4.

FERM BP-8364

2. SCIENTIFIC DESCRIPTION AND PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under 1 above was accompanied by:

- a scientific description
- a proposed taxonomic designation

3. RECEIPT AND ACCEPTANCE

This International Depository Authority accepts the microorganism identified under 1 above, which was received by it on April 23, 2003 (date of the original deposit).

4. RECEIPT OF REQUEST FOR CONVERSION

This International Depository Authority accepted the microorganism identified under 1 above, which was received by it on - - - - - (date of the original deposit), and received a request for conversion to a deposit under the Budapest Treaty from the original deposit on - - - - -.

5. INTERNATIONAL DEPOSITORY AUTHORITY

Name: International Patent Organism Depository
National Institute of Advanced Industrial Science and Technology
Dr. Syuichi Oka, DIRECTOR Date: April 23, 2003

Address: AIST Tsukuba Central 6, 1-1, Higashi 1-Chome Tsukuba-shi, Ibaraki-ken
305-8566, JAPAN

番式 8 (第7条第1項関係)

[特許手続上の微生物の寄託の国際的承認
に関するブダペスト条約]

下記国際寄託当局によって規則7. 1に従い
発行される。

原寄託についての受託証

氏名（名称） 武田薬品工業株式会社
寄託者 代表者 武田 國男
あて名 大阪市中央区道修町四丁目1番1号

殿

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT

issued pursuant to Rule 7.1 by the INTERNATIONAL DEPOSITORY AUTHORITY identified at the bottom of this page.

1. 微生物の表示	
(寄託者が付した識別のための表示) A h W 2 3 N 3 H 3 E 4	(受託番号) FERM BP- 8364
2. 科学的性質及び分類学上の位置	
1 植の微生物には、次の事項を記載した文書が添付されていた。 <input checked="" type="checkbox"/> 科学的性質 <input checked="" type="checkbox"/> 分類学上の位置	
3. 受領及び受託	
本国際寄託当局は、平成 15 年 4 月 23 日（原寄託日）に受領した1植の微生物を受託する。	
4. 移管請求の受領	
本国際寄託当局は、 年 月 日（原寄託日）に1植の微生物を受領した。 そして、 年 月 日に原寄託よりブダペスト条約に基づく寄託への移管請求を受領した。	
5. 国際寄託当局	
独立行政法人産業技術総合研究所 特許生物寄託センター International Patent Organization Depository 名称： National Institute of Advanced Industrial Science and Technology センター長 岡 修 Dr. Syuichi Oka, Director	
あて名： 日本国茨城県つくば市東1丁目1番地1 中央第6（郵便番号 305-8566） AIST Tsukuba Central 6, 1-1, Higashi 1-Chome Tsukuba-shi, Ibaraki-ken 305-8566 Japan	
平成15年(2003) 4月23日	

BUDAPEST TREATY ON THE INTERNATIONAL
RECOGNITION OF THE DEPOSIT OF MICROORGANISMS
FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT
issued pursuant to Rule 7.1 by the
INTERNATIONAL DEPOSITORY AUTHORITY
identified at the bottom of this page

To: Depositor

Name: Takeda Pharmaceutical Company Limited
Kunio Takeda
Representative

Address: 1-1, Doshomachi 4-chome, Chuo-ku, Osaka-shi

1. IDENTIFICATION OF THE MICROORGANISM

Identification reference given by the DEPOSITOR: Accession number given by the INTERNATIONAL DEPOSITORY AUTHORITY

AhW23N2G6D1

FERM BP-8363

2. SCIENTIFIC DESCRIPTION AND PROPOSED TAXONOMIC DESIGNATION

The microorganism identified under 1 above was accompanied by:

a scientific description
 a proposed taxonomic designation

3. RECEIPT AND ACCEPTANCE

This International Depository Authority accepts the microorganism identified under 1 above, which was received by it on April 23, 2003 (date of the original deposit).

4. RECEIPT OF REQUEST FOR CONVERSION

This International Depository Authority accepted the microorganism identified under 1 above, which was received by it on - - - - - (date of the original deposit), and received a request for conversion to a deposit under the Budapest Treaty from the original deposit on - - - - -.

5. INTERNATIONAL DEPOSITORY AUTHORITY

Name: International Patent Organism Depository
National Institute of Advanced Industrial Science and Technology
Dr. Syuichi Oka, DIRECTOR Date: April 23, 2003

Address: AIST Tsukuba Central 6, 1-1, Higashi 1-Chome Tsukuba-shi, Ibaraki-ken
305-8566, JAPAN

番式 8 (第7条第1項関係)

[特許手続上の微生物の寄託の国際的承認
に関するブダペスト条約]

下記国際寄託当局によって規則7. 1に従い
発行される。

原寄託についての受託証

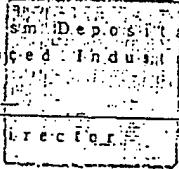
氏名 (名称) 武田薬品工業株式会社
寄託者 代表者 武田 國男
あて名 大阪市中央区道修町四丁目1番1号

殿

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT

issued pursuant to Rule 7.1 by the INTERNATIONAL DEPOSITORY AUTHORITY identified at the bottom of this page.

1. 微生物の表示	
(寄託者が付した識別のための表示) AHW23N2G6D1	(受託番号) FERM BP- 8363
2. 科学的性質及び分類学上の位置	
1 梱の微生物には、次の事項を記載した文書が添付されていた。 <input checked="" type="checkbox"/> 科学的性質 <input checked="" type="checkbox"/> 分類学上の位置	
3. 受領及び受託	
本国際寄託当局は、平成 15 年 4 月 23 日 (原寄託日) に受領した 1 梱の微生物を受託する。	
4. 移管請求の受領	
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5. 国際寄託当局	
独立行政法人産業技術総合研究所 特許生物寄託センター International Patent Organization National Institute of Advanced Industrial Science and Technology International Depository Dr. Syuichi Oka, Director  あて名：日本国茨城県つくば市東1丁目1番地1 中央6号 (郵便番号 305-8566) AIST Tsukuba Central 6, 1-1, Higashi 1-Chome Tsukuba-shi, Ibaraki-ken 305-8566 Japan	
平成15年(2003) 4月23日	